SUMMARY MINUTES

OF THE

MICROBIOLOGY DEVICES PANEL MEETING

OPEN SESSION

OCTOBER 12, 2001

Gaithersburg Hilton Hotel
620 Perry Parkway
Gaithersburg, MD

CALL TO ORDER

Panel Chair Michael Wilson, MD, called the meeting to order at 9:04 AM and asked the panel members and consultants to introduce themselves. After she read the conflict of interest statement, **Panel Executive Secretary Freddie Poole** announced there were no conflicts of interest to report for any panel members or consultants for today's agenda.

NEW BUSINESS

PRESENTATION OF THE PREMARKET APPROVAL APPLICATION

P 010033: Cellestis Limited, QuantiFERON-TB. ***An in vitro diagnostic device for measuring the release of gamma-interferon from sensitized lymphocytes in PPD-stimulated whole blood. Intended as an aid in the diagnosis of latent tuberculosis infection and in the evaluation of individuals suspected of having M. tuberculosis.***

MANUFACTURER'S PRESENTATION

Jim Rothel, PhD, Chief Science Officer and Executive Director for Cellestis Ltd., provided an introduction for their presentation, a history of the development of the test and an overview of the test methodology, including its interpretation and its intended use.

Antonino Catanzaro, MD, identified as non-Executive Director of Cellestis, presented information on current diagnostic methods, the difficulties in diagnosing latent tuberculosis, and the shortcomings of the Tuberculin Skin Test (TST). He described some reasons for false negative results and major problems with the test, and concluded by describing the main advantages of QuantiFERON-TB (QTF).

Paul Wood, PhD, Director, Global Research and Development, Animal Health, CSL Limited, summarized the scientific basis for the QFT, an in vitro interferon blood test for cattle. He stated that bovine TB is a very good model for human TB. An avian

mycobacterium PPD provided a control for the bovine test as for the QFT. He concluded that the test was widely used in 11 countries in more than 150,000 animals, the test was found to be applicable to other mammals, including humans, and has provided an extensive validation of the QFT technology.

Jim Rothel, Ph.D., Chief Scientific Officer, Cellestis Limited, outlined the study design and clinical studies of QuantiFERON-TB in Australia and the US. The limits of detection for the test were established from the clinical trials completed in Australia. The CDC and the Walter Reed Army Institute of Research (WRAIR) carried out pivotal studies in the US. The patients were stratified into four groups by CDC, low risk group, medium to high risk group, patients suspected of having active TB, and patients with prior treatment for TB. WRAIR stratified their subjects into three groups; no identified risk factors, limited risk factors, and identified risk factors. He concluded that although there was no gold standard for latent tuberculosis infections, comparisons to TST demonstrated that the QFT is safe and effective for use.

Dr. Wilson invited the panel to ask questions of the sponsor. The panel members asked for clarification on the role of mitogens, cut off levels for the three risk groups, validity of the test in children and immune compromised patients (particularly HIV patients), anticoagulation of the whole blood sample, false positives (particularly in the low risk group), problems of BCG exposure, non-tuberculosis mycobacterium, avian antigen stimulations, and assay specificity.

The company responded to the questions asked. They stated that children and immuno-compromised patients are not included in this study, but additional studies would be collected and submitted to the agency. Heparin is the only anticoagulant employed for sample coagulation. They also addressed BCG exposure and avian stimulations and assay specificity.

FDA PRESENTATION

Roxanne G. Shively, MS, Senior Scientific Reviewer, Bacteriology Devices Branch, presented FDA concerns with the QFT analytical performance, and similarities and differences with the QFT and the TST. She stated that there were no independent

standards outside the kit materials and no external control are provided with QFT. The cut off levels established for QFT are very important in ultimately controlling TB in the general population. During the studies of QFT, inter-laboratory reproducibility was not established.

Leonard Sacks, MD, Senior Staff Fellow, Division of Special Pathogens and Immunological Drug Products, Center for Drug Evaluation and Research, presented the clinical review of the PMA. He explained that QuantiFERON-TB assay is intended for use in the detection of latent *Mycobacterium tuberculosis* infection; however, a negative test does not preclude active TB. Since no definite gold standard for the diagnosis of latent TB exists, the sponsor compared their test with TST and correlated the results of their test with the risk for TB.

He presented the FDA's clinical analysis of the performance of the assay in high risk and low risk populations enrolled in the CDC and the WRAIR studies. He concluded that the positive rates for QFT were higher than TST in low risk populations. The pivotal clinical studies did not determine whether this was an indication of poorer specificity or increased sensitivity of QFT. The populations identified as positive by QFT or positive by TST often differed.

John Dawson, MS, JD, Mathematical Statistician in the Division of Statistics, Office of Surveillance and Biometrics, CDRH, presented the FDA's statistical analysis of the data. He explained that if one accepts that there is no gold standard, then we have no other option than comparing the QFT to TST in terms of agreement. However, prevalence is a confounding factor in any measurement of agreement. When overall agreement and confidence intervals are calculated for the three risk groups, the low and intermediate groups show a much more even distribution of cases and the least variance from prevalence. He concluded that overall agreement, the measure least affected by prevalence is at least 80% in the intended-use risk groups.

Dr. Wilson invited the panel to ask the sponsor and the FDA questions. The major issues discussed were: the effect of the cut-off point in the low risk group on the number of positive patients found by the QuantiFERON test and the resolution of the discordance question.

OPEN PUBLIC HEARING

James McAuley, MD, Medical Director, Cermak, Cook County Jail, Illinois presented the challenges in testing this population for tuberculosis. Jails are pass-through facilities of incarceration that can function as foci for transmission of infectious disease. Approximately 75% of the TB skin tests that he performs are not read due to the rapid turn over in the jail population. He concluded that in a correctional setting, a test that performed comparable to the current test (TST) would be preferable for TB treatment and elimination.

Stanley Reynolds read a letter from William Barry, Director of the TB Control Program, State Department of Health Laboratory, Pennsylvania, who expressed that the QFT would be an improvement to the TST and that it could be conducted in a standard medical laboratory as well as in public health laboratories.

OPEN COMMITTEE DISCUSSION

Dr. Wilson initiated the committee discussion by inviting the panel to first address the FDA's questions.

Question #1. Do the data from the two U.S. studies provide sufficient information on the performance of the QuantiFERON-TB assay? Are there other types of data or other types of analysis that can supplement those studies?

Dr. Charache suggested stratifying data by age and gender, and possible adjusting cutoffs based on differences. Dr. Baron suggested also looking at patients with pulmonary disease other than tuberculosis. Dr. Nolte suggested that studies on HIV patients would be helpful in the package insert since it could be used in those populations; and Dr. Durack recommended pediatric populations be added also. Dr. Beavis also recommended that additional reproducibility studies be performed at different laboratories.

The sponsor responded that they did not have enough data on HIV patients and they will come back with supplements for pediatric populations and perhaps HIV patients.

Question #2. Testing of control material is not available to compare results between sites in the clinical studies. Are the manufacturer's procedural and specimen controls adequate to ensure reliability and reproducibility of QFT testing between laboratories?

Dr. Lewinsohn felt that the standard curve for the QFT tests could function as the external control since there were no other alternatives besides the specimen control and the procedural control. Drs. Nolte and Charache were concerned about the lack of negative samples in the reproducibility studies, and recommended that additional studies be performed.

Question #3. In which populations of individuals could a positive or negative QuantiFERON-TB assay provide clinical utility alone or in conjunction with TST? Are there labeling restrictions, if any that would add to clinical utility for any population groups?

Drs. Baron and Nolte suggested that appropriate labeling restrictions are added to the package insert for immuno-compromised individuals, especially HIV patients, and children. Drs. Cockerill and Reller suggested that transplant populations might provide valuable information on mitogen-negative patients.

Question #4. When the QuantiFERON-TB assay is positive or negative, and not used in conjunction with TST, can available types of data from the two clinical studies be used to interpret the probability of TB infection for individuals with no known risk factors, moderate risk and high risk?

Dr. Nolte suggested that the performance characteristics relative to the three risk group be used for interpretation of data. Dr. Ng suggested that a visual interpretation such as the Venn diagrams used in the presentation of Dr. Sacks be included in the package insert. Dr. Charache suggested addressing false positive tests in the physician's instructions. There were additional discussions on the value of the QFT alone or done in conjunction with the TST and its use in low risk and high-risk groups. It was

recommended that the sponsor review data for 15 and 30% cutoff for each risk group and determine whether they should be adjusted.

Question #5. Could conjunctive or adjunctive use of QFT with TST provide additional benefit in any of the above risk groups?

The panel agreed that the labeling should contain some recommendations for using the QFT; however no guidance specific guidance should be included on use of the TST. However, clear definitions of low risk and high-risk patients may provide guidance for the clinician.

OPEN PUBLIC HEARING

Dr. Wilson opened the meeting to the general public. No one came forward at this time. The Open Public Hearing session was closed.

INDUSTRY RESPONSE

The sponsor had no additional comments.

FDA RESPONSE

The FDA had no further comments.

Dr. Nolte asked whether the CDC had any recommendations on how to interpret the QFT and Dr. Ng asked about inter-laboratory reproducibility data.

Gerry Mazurek, CDC, was recognized by the Chair and responded that the CDC was currently working on those recommendations. He also stated that the CDC would include reproducibility and inter-laboratory variations into account when assessing the QFT assay.

FINAL RECOMMENDATIONS AND VOTE

Freddie Poole read the voting options for a premarket approval application and identified the voting and temporary voting members of the panel. It was moved and seconded that QuantiFERON-TB be approvable with the following conditions:

(1) Statistical modeling of the data analysis to support use of an altered cutoff, as suggested by the FDA statistician,

(2) Stratification of the data by risk groups, gender, and age, with different cut-off values,

(3) Additional inter-laboratory reproducibility studies and variability, including negative samples, to include a range of expected values and negative samples representative of risk groups who would be tested,

(4) Interpretation of results and recommendations for use of the test provided in the labeling for the laboratory users along with separate recommendations for physician (physician education). CDC guidelines for testing to be incorporated in the package insert,

(5) Risk groups data analysis presented in the package insert to show not only 2x2 tables for each risk group, but also overlap between tuberculin skin test (TST) and QFT, e.g. Venn diagrams. Data on agreement of low risk positives and negative in 2x2 tables,

(6) The Labeling should be modified to include warnings or limitations for performing the QFT after administration of the (TST), and

(7) Explicit directions for use of the QFT with various risk groups should be based on data present; use with specific groups not evaluated should be focus of subsequent data.

The panel members then stated their reasons for voting for approvable with conditions for the QuantiFERON-TB.

Dr. Wilson thanked the sponsor for a well-done presentation, and the panel members, consultants and the FDA for their participation. He adjourned the meeting at 2:36 PM.

I certify that I attended the Meeting of the Microbiology Devices Panel on October 11 & 12, 2001 and that this summary accurately reflects what transpired.

Freddie Mae Moody Poole
Executive Secretary
Microbiology Panel

I approve the minutes of this meeting
As recorded in this summary.

Michael L. Wilson, MD

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